shear mixer granulator.

REMARKS

Claims 1-10, 12-50 and 76-94 are pending in the present Application.

By the present amendment, one (1) claim is cancelled, eleven (11) dependent claims are added, and one (1) independent claim and six (6) dependent claims are amended.

Claim 1, by amendment thereof, incorporates subject matter that finds support in the specification at least at page 4, line 30, and that further is the subject of Claim 11, now cancelled. By insertion of the words "discrete solid" immediately before "orally deliverable dose units", Claim 1 and all claims dependent therefrom are now focused more specifically on solid dosage forms such as tablets, capsules, *etc*. This amendment therefore brings all claims presently in consideration more uniformly into line with Group I as identified in the restriction requirement (Office Action of August 21, 2000).

Further, Claim 1, by amendment thereof, no longer incorporates an explicit requirement that "a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib having at least one of

(a) a time to reach 100 ng/ml not greater than about 0.5 h after administration;

(b) a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration;

(c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;

(d) a terminal half-life ($T_{1/2}$) not less than about 10 h; and

(e) a maximum concentration (C_{max}) not less than about 200 ng/ml."

In this regard, Applicant notes that terminal half-life ($T_{1/2}$) is a property of the drug itself, in this case celecoxib, that is not significantly modified by the nature of the formulation or dosage form. A terminal half-life not less than about 10 h is a property of celecoxib regardless of how formulated, thus recitation of "at least one of" a series of pharmacokinetic parameters including terminal half-life does not meaningfully limit scope of the claim. Deletion of this recitation therefore does not result in expansion of claim scope, but removes a redundancy and thereby enhances clarity of the claim.

Claims 2-5 are amended, without effect on meaning or scope of these claims, to enhance clarity, as necessitated by amendment of Claim 1, from which these claims depend.

Claim 11 is cancelled as its subject matter is now the subject of amended Claim 1.

Claims 12 and 13 are amended to adjust dependency, as necessitated by cancellation of Claim 11. Claim 12 is also amended to clarify definition of a Markush group.

Claims 84-90 are added to define certain compositions of the invention with greater specificity. Claim 84, which recites a relative bioavailability not less than about 70%, finds support in the specification at least at page 7, line 6. Claims 85-88, which recite maximum D_{90} celecoxib particle sizes of 200 μm, 100 μm, 40 μm and 25 μm respectively, find support in the specification at least at page 7, lines 15-20. Claims 89 and 90, which recite mean celecoxib particle sizes of about 1 μm to about 10 μm and about 5 μm to about 7 μm respectively, find support in the specification at least at page 7, lines 22-24.

Claims 91-94 are added to define certain methods to make compositions of the invention with greater specificity. Claim 91, which recites cooling of the celecoxib during milling, and Claim 92, which recites that said cooling is effected using liquid nitrogen, find support in the specification at least at page 34, lines 6-8. Claim 93, which recites operation of a pin mill with counter rotating disks, finds support in the specification at least at page 56, lines 1-2. Claim 94, which recites wet granulation in a high shear mixer/granulator, finds support in the specification at least at page 34, lines 13-14.

No new matter is introduced and no change in inventorship results from the amendments proposed herein.

RESPONSE TO OFFICE ACTION DATED AUGUST 31, 2001

Claims 1-50 and 77-80, of which all except Claim 11 remain in consideration following the present amendment, stand rejected in the above-identified Application. Claims 76 and 81-83 are objected to as being dependent on a rejected base claim but have been found allowable if rewritten in independent form including all limitations of the base claim and any intervening claims.

1. Rejection of Claims 1-50 under 35 USC §103(a)

Claims 1-50, of which Claims 1-10 and 12-50 remain in consideration following the present amendment, are rejected under 35 USC §103(a) as being unpatentable over Black (EP 0 863 134). This rejection is respectfully traversed.

A. A *prima facie* case of obviousness has not been made

It is respectfully submitted that the Examiner has failed to make a *prima facie* case of obviousness of the present claims over Black. See M.P.E.P. 2143, first paragraph, relating to criteria for establishment of a *prima facie* case of obviousness: "... the prior art reference ... must teach or suggest all the claim limitations."

Black neither teaches nor suggests replacement of his compound 2-(3,5-difluorophenyl)-3-(4-(methyl-sulfonyl)phenyl)-2-cyclopenten-1-one by any other selective COX-2 inhibitory drug, much less by the specific selective COX-2 inhibitory drug celecoxib. The Examiner agrees "the reference is silent as to the teaching of celecoxib" but goes on to state that "it would have been *prima facie* obvious for one of skill in the art, by routine experimentation" to determine a suitable COX-2 inhibitor to treat COX-2 mediated diseases without adverse side effect in the gastrointestinal tract. This, however, was not the problem to be solved by the present invention. Celecoxib is a known selective COX-2 inhibitory drug, known to have reduced potential for gastrointestinal side effects. A problem faced by the present inventors was to provide pharmaceutically acceptable formulations of this drug having high relative bioavailability in spite of the very low aqueous solubility of the drug. Black provides no teaching or suggestion related to bioavailability of his formulations. The present claims, as amended herein, recite "a relative bioavailability not less than about 50% by comparison with an orally delivered solution containing celecoxib at the same dosage rate," on which Black is silent. Thus at least one of the essential criteria for establishment of a *prima facie* case of obviousness set forth in M.P.E.P. 2143 is absent.

B. Even if a *prima facie* case of obviousness were made, evidence exists to rebut it

B.1. The art teaches that drugs of low solubility tend to exhibit low bioavailability

It was part of common general knowledge among those of skill in the art at the time the present invention was made that poorly soluble drugs, if orally administered in particulate form, tend to exhibit low bioavailability, because the dissolution process in the gastrointestinal tract is a rate-limiting step in the absorption process for such drugs. See, for example, in the standard textbook Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th edition, by Ansel *et al.* (1995), at pages 61-62 (copy enclosed herewith for the Examiner's convenience), in the paragraph bridging those pages:

> ... [I]f the rate of dissolution for a drug particle is slow, as may be due to

> the physiochemical [*sic*, physicochemical] characteristics of the drug substance or the dosage form, the dissolution process itself would be a rate-limiting step in the absorption process. Slowly soluble drugs such as digoxin may not only be absorbed at a slow rate, they may be incompletely absorbed, or in some cases largely unabsorbed, following oral administration ... . Thus, poorly soluble drugs or poorly formulated drug products may result in a drug's incomplete absorption ... .

Celecoxib has a solubility in water of just 5 µg ml at 5-40°C, *i.e.*, 200,000 parts of water are needed to dissolve 1 part of celecoxib. This places celecoxib in the category "practically insoluble" or "insoluble" as defined in the U.S. Pharmacopeia (USP 24, p. 2254, copy attached for the Examiner's convenience), as requiring more than 10,000 parts of solvent per part of solute.

At least some degree of predictability is required for a finding of obviousness. M.P.E.P. 2143.02, second paragraph. As demonstrated by extrinsic evidence (Ansel) cited immediately above, any predictability that exists does <u>not</u> lead to an expectation of high bioavailability for a practically insoluble drug such as celecoxib, when formulated as particulate material in a solid dosage form as recited in the present claims.

Furthermore, Ansel <u>teaches away</u> from the present invention by predicting that celecoxib, practically insoluble drug, would be poorly absorbed if orally administered as particulate material in a solid dosage form, and would therefore show low relative bioavailability by comparison with the same dose of celecoxib orally administered in solution in a suitable solvent. Indeed, when unformulated celecoxib is administered orally in a capsule, relative bioavailability is low. See the present specification at page 47, Table 11-1, wherein unformulated celecoxib has an <u>absolute</u> bioavailability of 16.9%, by comparison with an oral solution of celecoxib in a suitable solvent, which has an <u>absolute</u> bioavailability of 57.1%. In this example, the <u>relative</u> bioavailability of unformulated celecoxib is only 16.9/57.1, or 29.6%. However, contrary to the Ansel prediction, relative bioavailabilities of 50% or greater have been found by the present inventors when celecoxib is formulated according to the invention. "Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." M.P.E.P. 2145, X, *D*, 3, first paragraph.

B.2. Impermissible hindsight has been used in making the rejection

The Examiner has cited no evidence conflicting with that of Ansel, cited above, that would suggest predictability of high relative bioavailability of a practically insoluble drug such as celecoxib when orally administered in particulate form in a solid formulation such as a tablet or capsule. Thus the statement that "it would have been obvious for one of the ordinary skill in this art to, by routine experimentation, determine a suitable bioavailability rate of the compound" is based on hindsight and is impermissible. M.P.E.P. 2145, X, A.

B.3. Black's teaching of wetting agent does not render the present invention obvious

The Examiner cites Black's teaching of wetting agent in compositions comprising his compound 2-(3,5-difluorophenyl)-3-(4-(methyl-sulfonyl)phenyl)-2-cyclopenten-1-one as evidence that Black "does recognize the use of wetting agent in powder or granule formulation". Applicant does not dispute that wetting agents are common ingredients of drug formulations, but respectfully points out that Black gives no suggestion that use of such wetting agent can lead to relative bioavailability of about 50% or more, in the case of his compound. The Examiner attempts to shift the burden to Applicant to establish that Black's formulation does not have such a relative bioavailability; however, this is improper for the following reasons.

1. No *prima facie* case of obviousness has been made, as shown above.
2. Even if it were *prima facie* obvious from Black that use of a wetting agent would enhance bioavailability in the case of his compound (although no such suggestion is found in Black), it would still nonetheless be surprising in light of accepted wisdom (as evidenced by Ansel) if in the case of celecoxib, a compound of extremely low solubility, addition of a wetting agent could lead to a relative bioavailability of about 50% or more.
3. Even if Black's formulation were found to have a relative bioavailability of about 50% or more (which would be excessively onerous for Applicant to try to determine, having no ready source of Black's compound), it would not render obvious a formulation of celecoxib having such bioavailability, except perhaps in hindsight, which would be impermissible. The teaching in the art at the time the invention was made was clearly that, as evidenced by Ansel, a solid particulate formulation of a drug of such insolubility as celecoxib would tend to have low bioavailability.

B.3. The improper "obviousness to try" standard has been applied

The Examiner appears to imply that because Black discloses solid dosage forms of his compound, including tablets, troches, lozenges and capsules, in admixture with excipients, it would have been obvious for one of skill in the art at the time the present invention was made to have tried making similar dosage forms of celecoxib. This is an improper "obviousness to try" rationale made in support of an obviousness rejection. M.P.E.P. 2145, X, *B*.

The Examiner has failed to adequately consider the unexpected results set forth in the present specification, to which Applicant drew attention in its response dated March 23, 2001, in particular those results showing relative bioavailability of about 50% or more, for formulations of the invention as presently claimed. Even if one of ordinary skill might have found it obvious to make a formulation similar to one described by Black, but using celecoxib in place of Black's compound, it would not have been with the expectation that such high bioavailability would have been achievable, especially considering the extremely low solubility of celecoxib.

B.4. Secondary indicia of nonobviousness are present

The present invention represents a major contribution to the useful arts, at least in part by providing convenient discrete solid dosage forms of celecoxib suitable for oral administration, yet having high bioavailability relative to a solution of the drug, thereby avoiding the need for excessively high doses to compensate for poor absorption.

The great success of celecoxib capsules, marketed under the trademark Celebrex®, in providing a safe and effective therapy for osteoarthritis and other cyclooxygenase-2 mediated conditions to thousands of sufferers from such conditions, is in no small measure a consequence of the invention presently claimed.

No consideration has been given in the present Action to these secondary indicia of nonobviousness.

C. Nonobviousness is even more strongly supported for the claims as herein amended

Amendment of the claims as herein proposed is made to bring Claim 1 and all claims dependent therefrom more uniformly into line with Group I as identified in the restriction requirement (Office Action of August 21, 2000), and to remove a redundancy therefrom as indicated in the Remarks. This amendment is not required to overcome the 35 USC §103(a) rejection over Black; that rejection is traversed for reasons unaffected by the present amendment, and fully set out above.

However, with the recitation in Claim 1 that the orally deliverable dose units of a composition of the invention are in discrete solid form, as exemplified by tablets and capsules (Claim 13), the high relative bioavailability becomes an even more surprising and unexpected finding. See, for example, in the standard textbook Remington: The Science and Practice of Pharmacy, 19th edition, Volume 1, Chapter 43: Clinical Pharmacokinetics, by Rollins (1995), at page 742 (copy enclosed herewith for the Examiner's convenience), second column, second full paragraph:

> A drug usually has the highest bioavailability if administered orally as an aqueous solution; finely comminuted drugs in suspension follow closely. However, as a drug is packed into hard gelatin capsules or compacted into tablets, its bioavailability decreases.

Thus one of skill in the art at the time the invention was made would have been even less motivated to try formulating celecoxib as a capsule or tablet than, for example, as a suspension, as the expectation of acceptable bioavailability would have been even lower.

2. Objection to Claims 76 and 81-83

The subject matter of Claims 76 and 81-83 has been found allowable if rewritten in independent form. Applicant may later elect to present these claims in independent form; however, as the claims from which they depend remain in consideration, no amendment of Claims 76 and 81-83 is proposed at this time.

3. Rejection of Claims 77-80

Claims 77-80 are shown as rejected in the Office Action Summary but no basis for rejection of these claims is given in the Detailed Action. Applicant appreciates Examiner Tran's courtesy in a telephone conversation on October 16, 2001, during which the Examiner indicated that Claims 77-80 are in fact allowable as depending from Claim 76, if Claim 76 is rewritten in independent form. Withdrawal of the rejection of Claims 77-80 is therefore respectfully requested.

All claims presently in consideration are believed to be in condition for allowance.

Respectfully submitted,

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Attachments
Amended claims in marked-up form in compliance with 37 CFR §1.121(c)(1)(ii)
Fee Transmittal Sheet
Ansel (1995) reference cited in Response, part 2, B.1
USP 24 reference cited in Response, part 2, B.1
Rollins (1995) reference cited in Response, part 2, C
Form PTO-1449
Copies of art cited in IDS
Supplementary Partial European Search Report dated June 22, 2001

AMENDED CLAIMS IN MARKED-UP FORM IN COMPLIANCE WITH 37 CFR §1.121(c)(1)(ii)

1. (Amended) A pharmaceutical composition comprising one or more discrete solid orally deliverable dose units, each comprising particulate celecoxib in an amount of about 10 mg to about 1000 mg in intimate mixture with one or more pharmaceutically acceptable excipients, [wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib having at least one of

(a) a time to reach 100 ng/ml not greater than about 0.5 h after administration;

(b) a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration;

(c) a duration of time wherein concentration remains above 100 ng/ml not less than about 12 h;

(d) a terminal half-life ($T_{1/2}$) not less than about 12 h; and

(e) a maximum concentration (C_{max}) not less than about 200 ng/ml;]

said composition exhibiting upon oral administration a relative bioavailability not less than about 50% by comparison with an orally delivered solution containing celecoxib at the same dosage rate.

2. (Amended) The composition of Claim 1 wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib having a time to reach maximum concentration (T_{max}) not greater than about 3 h after administration.

3. (Amended) The composition of Claim 1 wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib having a time to reach maximum concentration (T_{max}) not greater than about 1.7 h after administration.

4. (Amended) The composition of Claim 1 wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib having a maximum concentration (C_{max}) not less than

about 200 ng ml.

5. (Amended) The composition of Claim 1 wherein a single dose unit, upon oral administration to a fasting subject, provides a time course of blood serum concentration of celecoxib having a maximum concentration (C_{max}) not less than about 400 ng ml.

12. (Amended) The composition of Claim [11] 1 wherein said [articles] discrete solid dose units are selected from the group consisting of tablets, pills, hard [or] and soft capsules, lozenges, sachets [or] and pastilles.

13. (Amended) The composition of Claim [11] 1 in [the] a form of unit dosage capsules or tablets.